Progress in Retinal and Eye Research xxx (2017) 1–12

Contents lists available at ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/prer

The role of systemic and topical fatty acids for dry eye treatment

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ARTICLE INFO

Article history:
Received 23 February 2017
Received in revised form
26 April 2017
Accepted 16 May 2017
Available online xxx

Keywords:
Dry eye disease
Ocular surface
Inflammation
Essential fatty acids

ABSTRACT

Dry eye is a prevalent condition and one of the main reasons for patients to seek ophthalmic medical care. A low systemic level of omega fatty acids is a risk factor for dry eye disease (DED). There are two groups of essential fatty acids (EFAs): the omega-6 (n-6) family and the omega-3 (n-3) family. Humans evolved on a diet in which the n-6:n-3 ratio was approximately 1:1, however the current Western diet tends to be deficient in n-3 EFAs and this ratio is typically much higher (approaching 17:1). The metabolism of EFAs generates four new families of local acting mediators: lipoxins, resolvins, protectins, and maresins. These molecules have anti-inflammatory and pro-resolution properties. We present a critical overview of animal model studies and human clinical trials that have shown that dietary modification and oral supplementation could be complementary therapeutic strategies for the treatment of dry eye. Furthermore, we discuss preliminary results of the topical application of n-3 and n-6 EFAs because these molecules may act as natural anti-inflammatory agents with positive changes of the entire ocular surface system.

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http://dx.doi.org/10.1016/j.preteyeres.2017.05.003
1350-9462/

1. Introduction

Dry eye disease (DED) is a common disorder of the ocular surface with a prevalence estimated to range between 5% and 34% of the population above the age of 50 years (DEWS, 2007a). Unfortunately, the quality of life of patients is often very poor because symptoms of DED interfere with daily activities such as driving, reading, carrying out professional work, using a computer, and watching television (Miljanović et al., 2007). Dry eye patients also report having role limitations, more pain, and less vitality than normal subjects (Mertzanis et al., 2005).

During the past 10 years, research in the area of DED has significantly increased, largely driven by the report of the Dry Eye Workshop (DEWS) of 2007 that did much to define, classify, and to recommend diagnostic criteria for the diagnosis of DED. The DEWS definition and classification subcommittee (DEWS, 2007b) put for the following definition of dry eye at that time, "Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface." Several risk factors for DED were proposed by the DEWS workshop including post-menopausal hormone therapy, sex hormones, low humidity environments, computer use, contact lens wear, refractive surgery, and low dietary consumption of essential fatty acids.

The traditional approach to treat dry eye focuses on tear replacement with artificial tears, or on conserving the patient's tears by means of occlusion of the tear drainage system or use of moisture-conserving spectacles. These therapies have been demonstrated to decrease symptoms and signs of dry eye, and improve the resultant blurred vision (Liu and Pflugfelder, 1999), but they can be considered palliative in that they do not address the immuno-inflammatory process that underlies the disease. In fact, a growing body of evidence suggests that chronic DED is characterized by an inflammatory process affecting the lacrimal gland-ocular surface functional unit. This inflammation is responsible for feeding a vicious cycle of tear insufficiency leading to ocular surface damage that in turn leads to symptoms and signs of chronic dry eye (Baudouin, 2007) (Barabino et al., 2012) (Baudouin et al., 2016). Although artificial tears can have an indirect anti-inflammatory effect by lowering tear osmolarity and diluting proinflammatory factors on the ocular surface, they cannot definitively interrupt this vicious cycle of inflammation-ocular surface damage in dry eye.

Topical and systemic anti-inflammatory agents, such as corticosteroids (Avunduk et al., 2003) (Pflugfelder et al., 2004) and cyclosporine A (Sall et al., 2000) (Kunert et al., 2002) have been reported to be effective in treating ocular surface symptoms and signs by reducing the infiltration of inflammatory cells in the lacrimal gland and/or the inflammatory cascade in the ocular surface. Use of anti-inflammatory therapy on a large scale is expected, but at present the well-known side effects of steroids (intraocular hypertension and cataract) and the efficacy of cyclosporin A, restricted to its influence on T-lymphocytes, are important limitations (Barabino and Dana, 2007).

Omega −3 and −6 are essential fatty acids (EFAs) critical for optimum ocular surface homeostasis. EFAs cannot be synthesized by the human body and, therefore, must be obtained from the diet. EFAs, once consumed, are modified by enzymes and may to produce anti-inflammatory agents (James et al., 2000). In the 80's Horrobin (1986) argued for a possible role of EFAs supplements in patients with Sjögren's syndrome and ocular surface damage and for many years only anecdotal case reports in the non-peer reviewed literature have described improvement in symptoms and signs of DED. More recently, numerous randomized placebo-controlled studies on the effects of systemic fatty acid in DED have been performed. The aim of this article is to analyze the characteristics of EFAs with particular regard to possible effects on the ocular surface system, to review the pre-clinical and clinical data available about their systemic use in DED, and to discuss new therapeutic applications such as the use of topical fatty acids.

2. Characteristics and biological effects of essential fatty acids

2.1. Structure and nomenclature of fatty acids

A fatty acid (FA) consists of a hydrocarbon chain (most commonly ranging in length from 12 to 24 carbons), with a methyl group at one end (omega end) and a carboxyl group at the other (alpha) end. They can be divided into two categories:

- Saturated fatty acids (FAs) with no double bonds.
- Unsaturated FAs with at least one double bond attached to the carbon chain.

Unsaturated fatty FAs can be further categorized as mono-or polyunsaturated, depending on the number of double bonds present. Polyunsaturated fatty acids (PUFAs) include a group of compounds called essential fatty acids (EFAs). These compounds are termed "essential" because the human organism needs them but lacks the appropriate enzymes for their synthesis. There are two families of EFAs: the omega-6 (n-6) family and the omega-3 (n-3) family. The two groups of compounds are not interchangeable and are required for normal human health (Simopoulos, 2002). The difference between them is the position of their first double bond. In n-6 EFAs, the first double bond is situated on the sixth carbon atom, while in n-3 EFAs, the first double bond is found on the third carbon atom, counting from the omega end, where the methyl group is located. Fatty acid nomenclature can be understood as follows: number of carbons, followed by a colon and the number of double bonds, which is then followed by the position of the first double bond counting from the omega carbon. For example, the lipid name for alpha-linolenic acid (ALA) is 18:3 n-3. It contains 18 carbons and 3 double bonds, and the first double bond is three carbon atoms from the omega end.

The EFAs of the n-6 family include linoleic acid (LA) (Fig. 1), which is the precursor to γ-linolenic acid (GLA), dihomo-γ-linolenic acid (DGLA) and arachidonic acid (AA). The n-3 EFAs include α-linolenic acid (ALA) (Fig. 2), which is the precursor to eicosapentaenoic acid (EPA), which then gives rise to docosahexaenoic acid (DHA) (Das, 2006) (Table 1). Dietary LA and ALA are metabolized by the enzymes Δ^6 and Δ^5 desaturases and elongases (Fig. 3). The purpose of desaturases is to remove two hydrogens, whereas elongases is to add two carbons. A number of factors are known to influence the activities of desaturases and elongases involved in the metabolism of EFAs. Saturated fats, alcohol, cholesterol, adrenaline, glucocorticoid, and nutritional deficiencies of vitamins and minerals (zinc, cobalt, etc.) inhibit Δ^6 and Δ^5 desaturases. Patients with diabetes and hypertension have reduced Δ^6 desaturase activity (Brenner, 1981). It appears that enzymes prefer to metabolize n-3 before n-6 (Das, 2006). Humans do not efficiently convert ALA to long chain EPA or DHA. The conversion rate of ALA to EPA in humans is estimated at only 5%–8%, and the conversion rate from EPA to DHA is even lower (0.1%–0.5%) (Jump, 2002).

2.2. Dietary sources of essential fatty acids

It has been proposed that humans evolved on a diet in which the n-6:n-3 ratio was approximately 1:1. Unfortunately, the current Western diet tends to be deficient in n-3 EFAs and today this ratio

Please cite this article in press as: Barabino, S., et al., The role of systemic and topical fatty acids for dry eye treatment, Progress in Retinal and Eye Research (2017), http://dx.doi.org/10.1016/j.preteyeres.2017.05.003